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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,286	04/20/2001	Jacques Dumas	BAYER-14	9096

23599 7590 11/30/2004

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,286	DUMAS ET AL.	
	Examiner	Art Unit	
	Brian S Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 39-74* is/are pending in the application.

4a) Of the above claim(s) *26,39-49,51 and 57-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/14/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions Acknowledged

1. Acknowledgment is made of applicant's election of N-(4-tert-butylpyridinyl)-N'-(4)-4-methoxyphenoxy)phenyl)urea and/or rheumatoid arthritis as the elected species. Applicant states that claims 36, 50 and 52-56 are readable on the elected species. However, the claim 36 has been cancelled by the applicant. Therefore, the examiner considers that only claims 50 and 52-56 are readable on the elected species, and will examined for the prosecution on the merits. Claims 26, 39-49, 51 and 57-74 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

2. Acknowledgement is made of applicant's filing of the instant application as a CIP of 09/778,039 filed 02/07/2001 ABN which is a CIP of 09/425,229 filed 10/22/1999 ABN which is a CON of 09/257,265 filed 02/25/1999 ABN which claims benefit of 60/115,878 filed 01/13/1999.

3. It is noted to applicant that the instantly claimed species N-(4-tert-butylpyridinyl)-N'-(4)-4-methoxyphenoxy)phenyl)urea was not disclosed until the filing of the instant application 09/838,286. Accordingly, the instant invention is examined to the scope of the instantly elected invention based on the filing date of 04/20/2001 as the priority date.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 50 and 52-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (i.e., rheumatoid arthritis, osteoarthritis and septic arthritis), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host", "the treatment of a disease other than cancer" with "a compound of Formula I ". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claimed invention is directed to a method for the therapeutic treatment of all types of diseases mediated by p38 including cancer (claims 50, 52-54) or all types of diseases mediated

by p38 other than cancer (claim 55), comprising administering said compounds represented by the Formula I.

The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and subsequently administering the instant composition. The instant specification discloses over 100 different types of diseases that are mediated by p38.

(2) The state of the prior art

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacotherapeutics.

With respect to the treatment of "disease mediated by p38 within a host" in claims 50 and 52-54, the scope of instant claims encompasses various diseases including cancer. For instance, in cancer therapy art, it is recognized that different types of cancers affect different organs and have different method of growth and harm the body. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or cancers mediated by p38.

With respect to the treatment of "a disease other than cancer", as stated above, the scope of the instant claims encompasses over 100 different types of diseases that may be related to p38 pathway mechanism. Although the specification links the p38 pathway signaling to numerous diseases, there is no proof or any competent evidence provided in the state art that inhibition of p38 leads to the effective treatment of the claimed disease conditions.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(5) The breadth of the claims

The instant claims embrace the therapeutic treatment of all diseases that are potentially mediated by p38 (claims 50, 52-54) and except cancers (claim 55).

The breadth of the claims is further exacerbated by the instantly claimed plethora of compounds that are represented by compound of Formula I.

(6) The amount of direction or guidance presented or (7) The presence or absence of working examples

The specification discloses that inhibition of p38 inhibits both cytokine production (eg., TNFα, IL-1, Il-6, IL-8) and proteolytic enzyme production (e.g., MMP-1, MMP-3). See page 2, lines 10-13. In addition, the specification discloses over 100 different types of diseases that are related to excessive levels of TNFα, excess or undesired matrix-destroying metalloprotease (MMP) activity or an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases. See page 2, line 14 thru page 5, line 17.

The specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of TNFα production (page 75).

As stated above, the instant invention correlates the involvement of p38 pathway mechanism in biosynthesis of various cytokines and proteolytic enzymes and their potential utility in the treatment of numerous diseases that are known to be mediated by one or more of the cytokines and proteolytic enzymes. However, the specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of the claimed disease conditions that are mediated by p38 without undue amount of experimentation.

(8) The quantity of experimentation necessary

Since the efficacy of the claimed compounds in treating complex diseases condition may have unrelated manifestation mentioned above or cancers due to p38 cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with

undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 50 and 52-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Base Claim 50 further limits that B can be a bridged cyclic structure of the formula-L(ML1)q, wherein L1 and L are each independently "thiophen, substituted thiophene, phenyl, substituted phenyl...with cyclic structure L bound directly to D". As stated above, the claim 50 provides sufficient definition for L, L1 and M. However, there is no definition of "q" in the claim 50. Applicant's failure to define "q" leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claims 52-56 are rejected herein because they are dependent on the rejected base claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 1-11, 14-17, 23 of copending U.S. Application No. 10/361858.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of referenced species of the genus or subgenus of the formula overlaps with the instantly claimed invention. Since the reference teaches the species of the genus or subgenus as having similar properties of the claimed invention, the reference makes obvious the claimed invention.

In looking in continuity data, it is noted that applicant has numerous issued patent and pending application encompassing the same or similar subject matter of the instant application. Applicant is aware of the patent and application is requested. Applicant review all subject matter considered same or similar, and submit the proper Terminal Disclaimer(s). For example, 09/776935, 10/086417 to be same or similar subject matter(s). The examiner's time to write each and every rejection is extremely burdensome.

Conclusion

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614